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1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/602,544	LIANG, LI-FANG	
	Examiner	Art Unit	
	Scott D. Long	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 June 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15* is/are rejected.

7)☒ Claim(s) *1, 6, 11* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *23 June 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/31/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claim Status

Claims 1-15 are pending. Claims 1-15 are under current examination.

Sequence Compliance

Sequence Listing and CRF have been received and are acknowledged by examiner. A statement that the Computer Readable Form (CRF) and the Sequence Listing are identical has been submitted and is acknowledged by examiner.

Oath/Declaration

The oath or declaration, having the signatures of all inventors, received on 23 June 2003 is in compliance with 37 CFR 1.63.

Information Disclosure Statement

The Information Disclosure Statements (IDS) filed on 31 May 2005 consisting of 2 sheets are in compliance with 37 CFR 1.97. Accordingly, examiner has considered the Information Disclosure Statements.

Priority

This application claims benefit as a CON of 09/632,879 (filed 08/04/2000 ABN) which is a DIV of 09/354,409 (filed 07/15/1999, issued PAT 6,555,672) which claims

benefit of 60/092,865 (filed 07/15/1998) and claims benefit of 60/123,270 (filed 03/08/1999). The instant application has been granted the benefit date, 15 July 1998, from the application 60/092,865.

Claim Objections

Claims 1, 6, and 11 are objected to because "GDF-8" is an indefinite term. The exact meaning of this term is not clear. It could have a few possible meanings. It could mean Geographic Data File. If it refers to Growth Differentiation Factor 8, then the objection can be overcome by inserting the full name into each independent claim prior the first occurrence of the term. Because the exact meaning of GDF-8 is not clear, clarification of this term is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-15 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: There seems to be a disconnect between the preamble, which is drawn to identifying a compound which regulates GDF-8 expression and the method steps which involve measuring the expression of an exogenous gene. If the method steps involve measuring luciferase, for example, then how can that data identify a compound that regulates GDF-8 expression? Wouldn't

there need to be a step where GDF-8 expression is measured? Regulation of GDF-8 expression is not really being measured by the currently claimed steps and therefore, the method is not exactly a method of identifying a compound with regulates GDF-8 expression. Clarification is required.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

WRITTEN DESCRIPTION

Claims 6-15 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The methodology for determining adequacy of Written Description to convey that applicant was in possession of the claimed invention includes determining whether the application describes an actual reduction to practice, determining whether the invention is complete as evidenced by drawings or determining whether the invention has been set forth in terms of distinguishing identifying characteristics as evidenced by other descriptions of the invention that are sufficiently detailed to show that applicant was in possession of the claimed invention (*Guidelines for Examination of Patent Applications*

under 35 USC § 112, p 1 "Written Description" Requirement; (Federal Register/Vol 66. No. 4, Friday, January 5, 2001; II Methodology for Determining Adequacy of Written Description (3.)).

Claims 6 and 11 are broadly drawn, such that they apply to methods of identifying compounds which regulate transcription from a genus of promoters comprising isolated nucleic acids which are at least 90% identical to SEQ ID NO:1. However, the working examples provided in the instant application only demonstrate methods of identifying compounds individual species of promoters, specifically SEQ ID NO: 1 and 4-9. In addition, Examples 3-4 describe the use of a few different truncations of SEQ ID NO:1, ranging from about 100 bp to about 650 bp.

The specification indicates that there is high homology between the human GDF-8 sequence and sequences from other vertebrates (page 17-18, specifically Table 1). While the promoters comprising the claimed methods of the instant application encompass the pig and mouse sequences, the claims also are broadly drawn such that they encompass numerous unknown sequences of different animal species. In addition, the important structural features of the promoter sequences claimed in the instant invention are not set forth in the instant application. Which portion of SEQ ID NO:1 is necessary for transcriptional activity? Which bases can be substituted and continue to have activity and conform to the claim limitations of a promoter having at least 90% identity to SEQ ID NO:1? MPEP § 2163, states "[A] biomolecule sequence described only by a functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient

identifying characteristic for written description purposes, ***even when accompanied by a method of obtaining the claimed sequence."***

The Revised Interim Guideline for Examination of Patent Applications under 35 USC § 112, p1 "Written Description" Requirement (Federal Register/ Vol 66. No 4, Friday January 5, 2001) states "THE CLAIMED INVENTION AS A WHOLE MAY NOT BE ADEQUATELY DESCRIBED IF THE CLAIMS REQUIRE AN ESSENTIAL OR CRITICAL ELEMENT WHICH IS NOT ADEQUATELY DESCRIBED IN THE SPECIFICATION AND WHICH IS NOT CONVENTIONAL IN THE ART" (column 3, page 71434), "WHEN THERE IS SUBSTANTIAL VARIATION WITHIN THE GENUS, ONE MUST DESCRIBE A SUFFICIENT VARIETY OF SPECIES TO REFLECT THE VARIATION WITHIN THE GENUS", "IN AN UNPREDICTABLE ART, ADEQUATE WRITTEN DESCRIPTION OF A GENUS WHICH EMBRACES WIDELY VARIANT SPECIES CANNOT BE ACHIEVED BY DISCLOSING ONLY ONE SPECIES WITHIN THE GENUS" (column 2, page 71436, emphasis added).

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "APPLICANT MUST CONVEY WITH REASONABLE CLARITY TO THOSE SKILLED IN THE ART THAT, AS OF THE FILING DATE SOUGHT, HE OR SHE WAS IN POSSESSION OF THE INVENTION. THE INVENTION IS, FOR PURPOSES OF THE 'WRITTEN DESCRIPTION' INQUIRY, *WHATEVER IS NOW CLAIMED*." (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize the [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Considering the potentially large numbers of polynucleotides encompassed by these method claims, the disclosure is not sufficient to show that a skilled artisan would recognize that the applicant was in possession of the claimed invention (genus) commensurate to its scope at the time the application was filed.

SCOPE OF ENABLEMENT

Claims 1-15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for *in vitro* methods of screening for modulators of GDF-8 promoter, does not reasonably provide enablement for *in vivo methods* of screening. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The Court in *Wands* states: "Enablement is not precluded by the necessity for some 'experimentation.'" Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working

examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a prima facie case is discussed below.

SCOPE OF THE INVENTION

The breadth of the claims encompasses a genus of methods of identifying a compound which regulates GDF-8 promoter comprising the nucleotide sequences of SEQ ID NO:1 (and homologous polynucleotides at least 90% identical to SEQ ID NO:1). As discussed supra, the specification fails to describe the *in vivo* methods that would read on this genus and would require undue experimentation to discover these methods. The specification only discloses and provides specific guidance for *in vitro* methods.

GUIDANCE & WORKING EXAMPLES

The specification does not provide specific guidance for or a working example for *in vivo* methods. In Example 4 (page 16, line 31-33), the specification indicates that expression constructs described in Examples 1-4 can be used to generate transgenic animals to demonstrate promoter activity *in vivo*. The specification (page 18, line 4) indicates that cells and cell lines of mouse, pig, and chicken origin can be used in the *in vivo* analysis of mouse, pig and chicken GDF-8 promoter, which expands the meaning of the limitation in claims 1, 6, and 11, wherein the method is practiced in a cultured cell.

The scope of the instant claims seems to encompass in vivo methods that utilize transgenic animals. Further, the specification (page 18, lines 4-14) indicate that the *in vivo* method can be practiced in mice, pigs, and chickens by generation of transgenic animals. The absence of working examples directed to *in vivo* methods necessitates further experimentation. Additionally, no working examples were provided that utilize transgenic animals. Therefore, the specification does not provide sufficient guidance on how to make and use *in vivo* methods of identifying a compound which regulates GDF-8 promoter comprising the nucleotide sequences of SEQ ID NO:1 (and homologous polynucleotides at least 90% identical to SEQ ID NO:1).

STATE OF THE ART & QUANTITY OF EXPERIMENTATION

Because the art of transgenic animals has for many years stated that the unpredictability lies with the site or sites of integration of the transgene into the target genome. Transgenic animals are regarded to have within their cells cellular mechanisms which prevent expression of the transgene, such as DNA methylation or deletion from the genome (Kappel et al (1992) Current Opinion in Biotechnology 3, 549, col. 2, parag. 2). Mullins et al (1993) states that not all animals express a transgene sufficiently to provide a model for a disease as the integration of a transgene into difference species of animal has been reported to given divergent phenotypes (Mullins et al (1993) Hypertension 22, page 631, col. 1, parag. 1, lines 14-17). The elements of the particular construct used to make transgenic animals are held to be critical, and that they must be designed case by case without general rules to obtain good expression of

a transgene; e.g., specific promoters, presence or absence of introns, etc. (Houdebine (1994) J. Biotech. 34, page 281). "The position effect" and unidentified control elements also are recognized to cause aberrant expression (Wall (1996) Theriogenology 45, 61, parag. 2, line 9 to page 62, line 3). Mullins et al. (J. Clin. Invest.1996; 98, page 1559) disclose that "the use of nonmurine species for transgenesis will continue to reflect the suitability of a particular species for the specific questions being addressed, bearing in mind that a given construct may react very differently from one species to another." Well-regulated transgenic expression is not frequently achieved because of poor levels or the complete absence of expression or leaky expression in non-target tissues (Cameron (1997) Molec. Biol. 7, page 256, col. 1 -2, bridg. parag.). Factors influencing low expression, or the lack their of, are not affected by copy number and such effects are seen in lines of transgenic mice made with the same construct (Cameron (1997), Molec. Biol. 7, page 256, lines 3-9). These factors, thus, are copy number independent and integration site dependent, emphasizing the role the integration site plays on expression of the transgene (Cameron (1997), Molec. Biol. 7, page 256, lines 10-13). Further, Sigmund (2000) states that the random nature of transgene insertion, resulting founder mice can contain the transgene at a different chromosomal site, and that the position of the transgene effects expression, and thus the observed phenotype (Sigmund (2000) Arteroscler. Throm. Vasc. Biol. 20, page 1426, col. 1, parag. 1, lines 1-7). With regard to the importance of promoter selection, Niemann (1998) states that transgenic pigs made with different promoters regulating expression of a growth hormone gene give disparate phenotypes - one deleterious to the pig, the other

compatible with pig health (Niemann (1998) Transg. Res. 7, page 73, col. 2, parag. 2, line 12 to page 73, col. 1, line 4). While, the intent is not to say that transgenic animals of a particular phenotype can never be made, the intent is to provide art taught reasoning as to why the instant claims are not enabled. Given such species differences in the expression of a transgene, particularly when taken with the lack of guidance in the specification for any transgenic non-human animal whose genome comprises a GDF-8 promoter (or variant of the GDF-8 promoter having at least 90% identity to SEQ ID NO:1), it would have required undue experimentation to predict the results achieved in any one host animal comprising the wide range of GDF-8 promoters encompassed by the scope of the claims, the levels of the transgene product, the consequences of that product, and therefore, the resulting phenotype. Further, while the specification describes the percent homology between the murine, porcine, chicken, and human GDF-8 promoters, the homology issue is not per se an indication that a generic mutated GDF-8 promoter (having 90% homology with SEQ ID NO:1, for example) could be reasonable predictive in the context of making and use of a heterologous transgenic mouse as broadly claimed, especially expression levels, structural/functional effect of the expression of an exogenous protein by the GDF-8 promoter, location of the expressed gene, positional effect and the pathways responsible for transgene expression are critical and complex factors which can not be reasonably predictive at the time the invention was made.

Moreover, the state of the art is such that ES cell technology is generally limited to the mouse system at present, and that only "putative" ES cells exist for other species

(see Moreadith *et al.*, J. Mol. Med., 1997, p. 214, S*ummary*). Note that "putative" ES cells lack a demonstration of the cell to give rise to germline tissue or the whole animal, a demonstration which is an art-recognized property of ES cells. Moreadith *et al.* supports this observation as they discuss the historical perspective of mouse ES cells as follows:

"The stage was set-one could grow normal, diploid ES cells in culture for multiple passages without loss of the ability to contribute to normal development. Furthermore, the cells contributed to the development of gametes at a high frequency (germline competence) and the haploid genomes of these cells were transmitted to the next generation. Thus, the introduction of mutations in these cells offered the possibility of producing mice with a predetermined genotype."

Such a demonstration has not been provided by the specification or the prior or post-filing art with regard to the generation of <u>any</u> species of animal ES cells, other than the mouse, which can give rise to the germline tissue of a developing animal. In addition, prior to the time of filing, Mullins *et al.* (Journal of Clinical Investigation, 1996) report that "although to date chimeric animals have been generated from several species including the pig, in no species other than the mouse has germline transmission of an ES cell been successfully demonstrated." (page 1558, column 2, first paragraph). As the claims are drawn to methods involving the manipulation of animal embryonic stem (ES), and particularly since the subject matter of the specification and the claimed invention encompasses the use of such cells for the generation of a transgenic animal,

the state of the art supports that only mouse ES cells were available for use for production of transgenic mice.

This is further supported by Pera *et al.* [Journal of Cell Science 113: 5-10 (2000)] who present the generic criteria for pluripotent ES or EG cells [see p. 6, 2nd column] and state that, "Thus far, only mouse EG or ES cells meet these generic criteria. Primate ES cells meet the first three of the four criteria, but not the last. Numerous other candidate mammalian ES cells have been described over the years in domestic and laboratory species, but only in the mouse have all criteria been met rigorously." [See p. 6, 2nd column, last paragraph].

CONCLUSION

In conclusion, given the breadth of the claims and the limited scope of the specification, an undue quantity of experimentation is require to make and use the invention beyond the scope of *in vitro* methods of identifying a compound which regulates GDF-8 promoter comprising the nucleotide sequences of SEQ ID NO:1 (and homologous polynucleotides at least 90% identical to SEQ ID NO:1).

Conclusion

No claims are allowed.

Examiner Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Scott Long** whose telephone number is **571-272-9048**. The examiner can normally be reached on Monday - Friday, 9am - 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joseph Woitach** can be reached on **571-272-0739**. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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